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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,128	BRIAND, JACQUES	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 are pending. Claims 12-16 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-11 and 17-19 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The rejections of Claims 1-11 and 17-19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn in view of applicant's arguments and amendments to the claims, entered 3/25/2005.

3. The rejection of Claim 19 under 35 U.S.C. 102(b) as being anticipated by Withers et al., (US 5,716,812) is withdrawn after further consideration, and in view of applicant's arguments, entered 03/25/2005.

4. The rejection of Claims 1, 2, 3, 10, 11, and 19 under rejected under 35 U.S.C. 102(b) as being anticipated by Deem et al., (WO 96/30849) is withdrawn after further consideration, and in view of applicant's arguments, entered 03/25/2005.

Priority

5. This application is the national stage entry of PCT/US00/26949, and claims benefit of Provisional application 60/156,557, filed 8/29/1999.

Information Disclosure Statement

6. The information disclosure statement filed 12/17/2004, has been considered. However, the reference of "Copy of Partial EP Search Report", although considered, has been crossed out because there is no recitation of a publication date.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1-4, 6, 7, 9-11, 17, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al., (US 2003/0143757). The rejection is maintained for the reasons of record, which are repeated for the convenience of the reader.

The claims are drawn to methods of identifying compounds that interact with a target molecule comprising the steps of: a) mixing a substrate, product or ligand of a target with at least one chemical compounds b) generating a first spectrum that displays either a chemical shift in the first dimension or a chemical shifts in the other dimension of substrate, product or ligand in step a); c) exposing substrate, product or ligand and mixture of chemical compounds in step a) to a target molecule for one or more incubation times; d) generating a second spectrum that displays either a chemical shifts in the first dimension or a chemical shifts in the other dimension of substrate or product in step a) that has been exposed to the target molecule in step c) in the presence of one or mixture of chemical compounds in step a); e) comparing said first spectrum and second spectrum after one or more said incubation times in step c) to determine at least one difference between said first spectrum and second spectrum, the differences observed along either or both chemical shift dimensions identifying the transformation of said substrate and classifying the presence of one or more compounds that are substrates, products or ligands that interact with said target molecule; and variations thereof.

Moore et al., (US 2003/0143757), at para [0052]-[0059], [0075]-[0082], [0139] teaches obtaining an NMR spectrum of a ligand, exposing the ligand to the target and generating a subsequent NMR spectrum of the ligand. Moore et al. state:

> According to one preferred embodiment, the determination of binding is achieved by the NMR method of line broadening, relaxation filtering or a combination of the two and comprises the steps of: i) obtaining a one-dimensional NMR spectrum of said drug core in the absence of said target; ii) mixing the target with the drug core at a molar ratio of between 1:1 and 1:100. iii) subjecting said mixture to nuclear magnetic resonance for a

period of time sufficient to obtain a one-dimensional spectrum; and iv) comparing the spectra obtained in steps i) and iii) to determine if said drug core has bound to said target.

Moore et al., (US 2003/0143757), at para [0052]-[0056]. Moore contemplates testing multiple drug cores in the same sample, which reads on mixing a substrate, product or ligand with at least one compound, and wherein the mixture comprises between 2 and 100 chemical compounds (claim 6). Moore contemplates targets that are protein, enzymes, peptides, nucleic acids, etc., which are biomolecules (claim 2). Moore teaches individual compartmentalization of compounds wherein the compounds are provided in multi-well plates, or attached to solid media or beads.

Response to Arguments

Applicant argues that the reference of Moore does not disclose exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Moore et al. do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing spectra of the target/compound/ligand mixture over time. Finally, Moore, et al. do not monitor a signal generated by a substrate, ligand or product over time. Instead, Moore et al. observe the signal of a chemical compound in a single mixture. Thus, Moore et al. do not identically show each and every element of the independent claims of this invention.

Applicant's arguments filed 03/25/2005 have been fully considered but they are not persuasive. Moore, throughout the publication, and for example, at p. 7, para [0076], disclose NMR analysis of multiple drug cores, reading on generating a spectrum of a mixture of a ligand and chemical compounds, and then generating a second spectrum after incubation of the mixture with target into to identify drug cores. Moore states: "The cross peaks for each individual drug core are then easily identifable as they appear at

the same frequencies as any two diagonal peaks corresponding to that drug core", (Moore at para [0076]).

8. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al., Proc. Natl. Acad. USA, Vol. 94, pp. 14249-14254 (Dec. 1997). The rejection is maintained for the reasons of record, which are repeated for the convenience of the reader.

Thompson et al. at the abstract, p. 14249, para 5-p. 14250, para 3, Fig. 1, p. 14252, para 3, Fig. 4, teach the proton NMR characterization of inhibitors of the cysteine protease, a biomolecule, wherein the inhibitors were synthesized with the isotope 3H; followed by NMR analysis of cathepsin K adducts with inhibitors, wherein the protease and inhibitors are incubated with 2-(*N*-morpholino)ethane-sulfonic acid (Mes)/NaCl/Cys for fixed times depending upon inhibitor concentration, whereupon the reactions are quenched by dialysation into 90% water/10% D_2O, 50 mM acetate-d_3, 250 mM NaCl, and 2mM L-Cys.

Response to Arguments

Applicant argues that the reference of Thompson does not disclose exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Thompson et al. do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing spectra of the target/compound/ligand mixture over time. Finally, Thompson et al. do not monitor a signal generated by a substrate, ligand or product over time. Instead, Thompson et al. observe the signal of a chemical compound in a single mixture. Thompson merely discloses a selectively double-labeled inhibitor alone or with cathepsin K. Applicant argues that a single sample was prepared for NMR analysis, as shown in Figure 4. Thus Thompson et al. do not identically show each and every element of the independent claims of this invention.

Applicant's arguments filed 03/25/2005 have been fully considered but they are not persuasive. Thompson et al. at p. 12250, para 3, teach that the samples for NMR are dialyzed into 90% water/10% D_2O, acetate-d_3, NaCl and L-Cys, which read on the at least one chemical compounds mixed with a ligands of the target. The examiner respectfully notes that the claims are broadly drawn to any chemical compound in the mixture.

9. Claims 1-11, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hajduk et al., J. Am. Chem. Soc. 1997, vol. 119, pp. 12257-12261 (IDS filed 2/27/02). The rejection is maintained for the reasons of record, which are repeated for the convenience of the reader.

Hajduk et al., throughout the publication, and at the abstract, p. 12257, para 2-p. 12258, Table 1, Figures 2-4, teach identifying compounds that bind to macromolecules by one-dimensional NMR, which exploits changes in either the relaxation rates or diffusion rates of a small compound, that occurs upon binding to the biomolecules. Hajduk et al., teaches a mixture of 2-phenylimidazole, which binds to the FK506 binding protein (FKBP) and eight compounds that do not bind to the protein; Figures 2-4 depict NMR plots of 1H NMR spectra for 2-phenylimidazole alone and binding to FKBP; and spectra for the ligand 5-cyano-4'hydroxybiphenyl, which binds to the matrix metalloproteinase stromelysin, and of said 5-cyano-4'hydroxybiphenyl binding to the catalytic domain of the proteolytic enzyme stromelysin. Hajduk et al. also teach 5-cyano-4'hydroxybiphenyl in combination with eight other compounds that do not bind stromelysin.

Response to Arguments

Applicant argues that the reference of Hajduk et al. does not disclose exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Hajduk et al. do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing spectra of the target/compound/ligand mixture over time. Finally, Hajduk et

al. do not monitor a signal generated by a substrate, ligand or product over time. Instead, Hajduk et al. observe the signal of a chemical compound in a single mixture. Thus Hajduk et al. do not identically show each and every element of the independent claims of this invention.

Applicant's arguments filed 03/25/2005 have been fully considered but they are not persuasive. Hajduk et al., at p. 12258, para 3-p. 12259, para 1, teach generating a spectrum of a mixture of test compounds (**1, 3-10**, see Figure 2), in the absence of the target FK506 binding protein (FKBP). Hajduk at p. 12258, para 4, states: "The signals corresponding to all of the compounds in the mixture (**1, 3-10**) appear in this spectrum." Next the spectrum of the test compounds in the presence of FKBP was obtained, and compared to the first spectra. "From this difference spectrum, the compound that binds to FKBP can be readily identified from an analysis of the chemical shifts which correspond to those of the free molecule". Thus Hajduk et al. anticipate the claimed invention.

10. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Fesik et al., (WO 98/48264). The rejection is maintained for the reasons of record, which are repeated for the convenience of the reader. It is noted that the claims were rejected over Fesik et al., (WO 98/48264) under 35 USC 102(b), which was an inadvertent mistake. As stated above, the claims are rejected under 35 USC 102 (a). The examiner regrets any inconvenience that this may have caused the applicant.

Fesik et al., (WO 98/48264), throughout the publication, and at p. 1, lines 2-4, p. 2, line 23-p. 3, line 12, p. 4, line 18-p.4, line 33, p. 7, line 32-p. 8, line 37, p. 10, lines 10-19, p. 10, line 35-p. 11, line 2, teaches: a) generating a first T2- or diffusion-filtered proton spectrum of one or a mixture of chemical compounds; b) exposing one or a mixture of chemical compounds to the target molecule; c) generating a second T2- or diffusion filtered proton spectrum of one or a mixture of chemical compounds that has been exposed to the target molecule in step (b); and d) comparing said first and second T2- or diffusion-filtered proton spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Additional steps comprise the steps of e) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture f) exposing each compound in the mixture individually to the target molecule, g) generating a T2- or diffusion-filtered proton spectrum of each compound in the mixture after exposure to the target molecule h) comparing each spectrum generated in step g) to the first spectrum generated from the target molecule alone to determine differences in any of those compared spectra, the differences identifying the presence of a compound that is a ligand which has bound to the target molecule; wherein the target is a polypeptide, which is a biomolecule. Fesik et al. teaches use of a sample changer with a total of 60 samples that can be run unattended and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data.

Response to Arguments

Applicant argues that the reference of Fesik (1998) does not disclose exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Fesik et al. (1998), do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing spectra of the target/compound/ligand mixture over time. Finally, Fesik et al. (1998), do not monitor a signal generated by a substrate, ligand or product over time. Instead, Fesik et al. examine only spectra of chemical compounds at a single time point, and not of substrate, ligand or product with chemical compound and target over time. Thus. Fesik et al. (1998), do not identically show each and every element of the independent claims of this invention.

Applicant's arguments filed 03/25/2005 have been fully considered but they are not persuasive. Fesik et al., (WO 98/48264), throughout the publication, and for example, at p. 1, lines 2-4, p. 2, line 23-p. 3, line 12, teach: a) generating a first T2- or

diffusion-filtered proton spectrum of one or a mixture of chemical compounds; b) exposing one or a mixture of chemical compounds to the target molecule; c) generating a second T2- or diffusion filtered proton spectrum of one or a mixture of chemical compounds that has been exposed to the target molecule in step (b); and d) comparing said first and second T2- or diffusion-filtered proton spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Thus Fesik (1998), anticipates the claimed invention.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the reference of Fesik (1998), examines only spectra of chemical compounds at a single time point, and not of substrate, ligand or product with chemical compound and target over time) do not correspond to limitations recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

11. Claims 1-4, 6, 7, 9-11, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fesik et al., (WO 97/18469). The rejection is maintained for the reasons of record, which are repeated for the convenience of the reader.

Fesik et al., (WO 97/18469), throughout the publication, and at p. 1, lines 2-4, p. 3, lines 7-28, p. 7, line 32-p. 8, line 2, p. 8, line 37-p. 9, line 28, p. 11, lines 32-36, p. 14, lines 10-17, p. 18, line 25-p. 31, line 9, teaches screening chemical compounds for binding to a given target biomolecule by a process involving the steps of a) first generating a first two-dimensional 15N/1H NMR correlation spectrum of a 15N-labeled target molecule; b) exposing the labeled target molecule to one or a mixture of chemical

compounds; c) next, generating a second two-dimensional 15N/1H NMR correlation spectrum of the labeled target molecule that has been exposed to one or a mixture of compounds in step (b); and d) comparing said first and second two dimensional15N/1 H NMR correlation spectra to determine differences between said first and said second spectra, the differences identifying the presence of one or more compounds that are ligands which have bound to the target molecule. Fesik et al. teaches use of a sample changer with a total of 60 samples that can be run unattended and computer programs to facilitate transfer and automatic processing of multiple one-dimensional NMR data. Fesik et al. teach that individual compounds, which may be interpreted as targets, that can be selected inter alia on the basis of size (molecular weight = 100-300) and molecular diversity. Compounds in the collection can have different shapes (e.g., flat aromatic rings(s), puckered aliphatic rings(s), straight and branched chain aliphatics with single, double, or triple bonds) and diverse functional groups (e.g., carboxylic acids, esters, ethers, amines, aldehydes, ketones, and various heterocyclic rings) for maximizing the possibility of discovering compounds that interact with widely diverse binding sites.

Response to Arguments

Applicant argues that the reference of Fesik (1997) does not disclose exposing substrate, ligand or product of a target molecule with chemical compounds and generating a spectrum of that mixture. Furthermore, Fesik et al. (1997), do not disclose exposing this mixture with a target molecule for one or more incubation times and comparing spectra of the target/compound/ligand mixture over time. Finally, Fesik et al. (1997), do not monitor a signal generated by a substrate, ligand or product over time. Instead, Fesik et al. (1997) examine only spectra of chemical compounds at a single time point, and not of substrate, ligand or product with chemical compound and target over time. Thus. Fesik et al. (1997), do not identically show each and every element of the independent claims of this invention.

Applicant's arguments filed 03/25/2005 have been fully considered but they are not persuasive. Fesik et al., (WO 97/18469), at p. 18, lines 24-37, teach mixing ^{15}N-labeled stromelysin (reading on a ligand), with chemical compounds that are acetohydroxamic acid, $CaCl_2$, sodium azide and TRIS buffered solution and generating a first spectrum, followed by exposing the mixture (absent evidence to the contrary), to

"test compounds", which read on targets. A second spectrum was generated, (see, also p. 7, line 32-p.8, line 9), to thereby identifying the stromelysin as binding to a test compound.

Conclusion

12. Claims 1-11 and 17-19 are rejected.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

ms

PADMASHRI PONNALURI
PRIMARY EXAMINER